

**REMARKS**

The applicants acknowledge with thanks the fact that the examiner has withdrawn the restriction requirement and agreed to examine all of the claims that are pending in this case.

**I. INTERVIEW SUMMARY**

The applicants thank Examiner Kubelik for the courtesy extended to T.K. Ball, David Fischhoff, and the undersigned attorney during an interview on August 1, 2007. The applicants affirm that the examiner's interview summary is accurate and provide the following additional remarks.

The examiner's interview summary indicates that the applicant would send the relevant portion of the Board decision regarding the date of invention. The board decision is of record in the image file wrapper, and the applicants have summarized the findings of the Board in the section below pertaining to unobviousness.

With respect to double patenting ("DP"), the examiner's interview summary specifies that the applicant will amend "other case." As discussed in greater detail below, amendments to the claims in co-pending application 10/102,469 render moot the double patenting rejection.

With respect to the term "reducing," the examiner's interview summary specifies "amend to say reduced relative to the starting sequence." As explained in more detail below, no such amendment is needed because this meaning of the claim is clear as presently worded.

With respect to the written description rejection relating to claim limitations that specify starting with a sequence derived from *Bacillus*, the examiner suggested during the interview that broader claims that did not specify *Bacillus* origin should render moot the particular basis for rejection. As explained in greater detail below, the applicants have traversed the rejection because it is improper. Nonetheless, the applicants have adopted the examiner's helpful suggestion and introduced new claims 120-141, which do not recite starting with sequences derived from *Bacillus*. These new claims otherwise largely correspond to claims 47, 50-51, 54-55, 63, 66-68, 107-109, 69, 73, 77, 79, 100-103, 105, respectively.

In the interview, the applicants also inquired about the status of their information disclosure statement (IDS) that was filed to disclose 305 documents that, generally speaking,

were from litigations involving the technology that is the subject of the present patent application (including litigations involving patents owned by the losing party to the interference in which this application was involved). The examiner confirmed that this IDS was in compliance with the rules for submission of documents for consideration by the Patent Office.

## II. EXPLANATION OF AMENDMENTS.

The amendments to claims 63-68, 112, and 117-118 are discussed below and are not intended to narrow the claims, or for reasons related to patentability. Rather, the amendments are intended to assure that the claims will be interpreted to their full intended scope.

The amendment to claim 55 corrects an obvious grammatical error.

As explained above, new claims 120-141 are essentially identical to pending claims except that they have been broadened so as not to specify *Bacillus* origin for the starting sequence(s). Although the application explains the invention primarily with respect to the preparation of synthetic plant genes which encode *Bacillus thuringiensis* crystal protein toxins, the application makes clear that this was done for brevity, and that the invention is intended to be much broader, applicable to essentially any proteins. (See paragraph spanning pages 16 and 17.) Thus, the broader claims find basis in the application as originally filed.

## III. INFORMATION DISCLOSURE STATEMENT ISSUES.

### A. Response to the Patent Office's missing file histories.

On page 2 of the office action, the examiner indicated that the Patent Office had lost file histories for three parent applications. In response, the applicants have recently filed copies of each of the file histories from the applicant's files. The applicants request that the examiner consider the parent file histories, and have listed them on a new PTO-1449 form for the record. Various patentability issues under 35 USC §§ 102, 103, and/or 112, first or second paragraphs, were raised by examiners in one or more of the parent applications. Although the applicants do not believe that any rejection from a parent application has merit, the applicants request that the examiner make any determination of relevance for herself with respect to the claims that are currently pending.

**B. Request for clarification concerning "litigation IDS"**

With respect to the information disclosure statement containing 305 litigation-related documents, a number of the documents were submitted under seal. A statement as to which documents were *not relevant* (and may properly be expunged at the conclusion of prosecution) would facilitate a fair treatment of the applicant's petition to expunge that was filed with this information disclosure statement and conditioned upon the relevance of the documents.

**IV. THE REJECTIONS THAT ALLEGED FAILURE TO COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT SHOULD BE WITHDRAWN.**

In paragraphs 4-5 of the office action, the Patent Office rejected claims 47-119 under 35 U.S.C. §112, first paragraph, alleging failure to comply with the written description requirement. The applicants respectfully traverse.

**A. The phrase "derived from *Bacillus*".**

The Patent Office alleged that neither the specification nor the originally filed claims provide the support for the phrase "derived from *Bacillus*." The applicants respectfully disagree.

This rejection is moot with respect to new claims 120-141, which do not contain the phrase at issue.

Original claim 18 recited, "A structural gene of claim 13 encoding an insecticidal protein *derived from B.t.k. ....*" (emphasis added.) B.t.k., of course, is a *Bacillus* bacteria. Thus, original claim 18 provides basis for the phrase in question. Similarly, claim 40 contained the phrase "derived from a *Bacillus thuringiensis* ...." Although claim 40 is not an original claim, after it was presented in this application, it withstood Board review in an *inter partes* interference proceeding.

The Patent Office further alleged, "nowhere in the specification or the originally filed claims is the starting material a derived sequence." To the contrary, all of the "starting material" sequences in the application are derived sequences. The plain meaning of the term

"derived" embraces obtaining something from a source. Thus, any wild type sequence obtained from a *Bacillus* with which one practices a method of the invention is a sequence that has been "derived from *Bacillus*."

As the Patent Office apparently recognizes, the term "derived from" is indicative of origin, but is not necessarily restricted to a wild type sequence due to, e.g., further human manipulation. Thus, for example, the truncated (or truncated and modified) B.t.k. HD-1 genes that are described in Example 1 (BglII fragment encoding amino acids 29-607 with a Met-Ala introduced at the N-terminus) and Example 2 (encoding amino acids 1-615) also are sequences "derived from *Bacillus*." Similarly, the fusion sequence used in Example 3 (see page 51), comprising codons for the amino-terminal two-thirds from a B.t.k. HD-1 gene fused to a carboxy-terminal one-third from a B.t.k. HD-73 gene represents another sequence (or sequences) "derived from *Bacillus*." (See page 53.) Example 3 also describes a number of other modified, truncated, and/or fusion gene constructs that are derived from *Bacillus*. The application contains other examples as well which will not be discussed here in detail, because the examples already mentioned provide ample evidence that the phrase "derived from *Bacillus*" has adequate basis in the application and the original claims and in the examples. Both wild type and manipulated coding sequences derived from *Bacillus* are exemplified.

#### **B. Any *Bacillus* species**

The Patent Office alleged, "Neither the instant specification nor the originally filed claims appear to provide support for the concept of the insecticidal protein coding sequence being from any *Bacillus* species. The specification indicates that insecticidal protein coding sequences only from *Bacillus thuringiensis* were considered...." The applicants respectfully disagree.

Although the application explains the invention primarily with respect to the preparation of synthetic plant genes which encode *Bacillus thuringiensis* crystal protein toxins, the application makes clear that this was done for brevity, and that the invention is intended to be much broader, applicable to essentially any proteins. (See paragraph spanning pages 16 and 17.)

The application teaches that the invention is generally applicable for making new structural genes for any protein,<sup>1</sup> and it is especially applicable for making structural genes for proteins derived from *Bacillus*, because bacteria of the genus *Bacillus* have genomes that are unusually rich in adenines and thymidines [(A+T)-rich]. (The specified problem sequences are themselves (A+T)-rich, and are apt to occur with greater frequency in an (A+T)-rich genome.) Support for claim recitations specifying insecticidal proteins derived from *Bacillus* may be found, e.g., at page 16, line 15, to page 17, line 9; and at page 21, line 1, to p. 22, line 12, which explain that the invention is particularly applicable to genes of *Bacillus*, which have among the most (A+T)-rich genomes and, consequently, a greater propensity for (A+T)-rich problem sequences.

This rejection is moot with respect to new claims 120-141, which do not contain the phrase at issue.

**C. Methods that involve reducing polyadenylation signals only, or reducing ATTTA sequences only.**

The Patent Office alleged, "Neither the instant specification or the originally filed claims appear to provide support for the concept of producing a coding sequence that is substantially devoid of polyadenylation signal sequences but not substantially devoid of ATTTA sequences and vice versa."

Indeed, some claims recite removal of ATTTA *or* polyadenylation signal sequences whereas others specify removal of both. These variations find support throughout the application, including at page 22, line 24, to p. 23, line 13. ("It is most preferred that substantially all the polyadenylation signals and ATTTA sequences are removed although enhanced expression levels are observed with only partial removal of either of the above identified sequences.") Also, original claim 1 was directed to a method and involved reducing the number of polyadenylation signal sequences recited in a Markush group that corresponds to the sequences listed in Table II. (See also claims 6-8.) Dependent claim 2 was further directed to reducing the number of ATTTA sequences, but this limitation was not present in claim 1 as

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<sup>1</sup> See, e.g., p. 17, lines 5-10 ("[I]t should be understood that the present method may be used to prepare synthetic plant genes which encode non-plant proteins other than the crystal protein toxin of *B.t.* as well as plant proteins . . .")

originally filed. Example 1 includes one embodiment in which the removal of only three polyadenylation signal sequences using mutagenesis primer BTK 240 (and no change in ATTAA sequences) resulted in dramatic increases in expression of the insecticidal protein in plant cells. Thus, both the specification as filed and the original claims provide support for the concept of removing the the polyadenylation signal sequences or the ATTAA sequences individually.

**D. Starting material being coding sequences that are portions of two or more insecticidal polypeptides (or hybrid sequences).**

The Patent Office alleged, "Neither the instant specification nor the originally filed claims appear to provide support for the starting material being coding sequences [that are] portions of two or more insecticidal polypeptides...." (claims 55 and 67.) Similarly, the Patent Office alleged that neither the specification nor original claims appeared to provide support for the starting material or protein being hybrids of at least two B.t. insecticidal proteins or their coding sequences (claims and 91-92); and the Patent Office alleged that neither the specification nor the original claims appeared to provide support for insecticidal protein being an insecticidal fusion (claim 114).

To the contrary, Example 3 describes experiments in which genes encoding chimeric insecticidal proteins were constructed using sequences derived from at least two different *Bacillus* insecticidal protein genes. For example, the inventors took the 5' two-thirds of a synthetic HD-1 gene and combined it with the 3' one-third of an HD-73 sequence, modified via site-directed mutagenesis. The resulting construct was devoid of ATTAA, and substantially devoid (reduced in this example from 18 to 2) of Table II polyadenylation signal sequences, and it encoded an *insecticidal hybrid protein* comprised of a fusion of fragments of more than one insecticidal protein derived from *Bacillus*. In fact, Example 3 contains multiple embodiments that involve truncations, fusions, and sequence modifications. Also, as noted above, the application explicitly states that, although much of the description pertains to *Bacillus thuringiensis* crystal proteins, that was done for brevity only, and the invention is intended to be applicable to essentially any other proteins. Thus, a person of ordinary skill in the field of the invention would understand that the methods of the invention were applicable to sequences that encode wild type proteins, variations thereof, truncations thereof, and fusions comprising portions of sequences derived from multiple sources, as all of these embodiments are exemplified in the application.

**E. Chloroplast transit peptide or secretion signal sequences.**

The Patent Office alleged that neither the specification nor the original claims provide support for using coding sequences for an amino-terminal chloroplast transit peptide or a secretion signal sequence. To the contrary, these elements finds support, e.g., at p. 32, lines 1-5, of the application, and in Examples 10 and 11.

**F. Designing a nucleotide sequence**

The Patent Office alleged that neither the specification nor the original claims appeared to provide support for "designing a nucleotide sequence" (a phrase that occurs and claims 113 and 117).

The basis for this rejection is unclear because a reader understands from the application that an aspect of the invention pertains to starting with a coding sequence and designing a modified coding sequence for construction of modified or synthetic structural genes with fewer "problem sequences" and better expression in plants. Explicit basis for the term "designing" occurs repeatedly in the application. For example, at page 31, lines 27-31, the application states, "In a particular embodiment of the present invention the enhancement method has been applied to design a modified and fully synthetic genes...." At the beginning of Example 2, it is explained that, "A syntheticB.t.k. HD-1 gene was designed...." (See page 45.) At the beginning of Example 3, the invention is again described in terms of "the algorithm used to design the synthetic HD-1 gene." (See page 51; see also page 59: "The C-terminal synthetic portion has been designed to eliminate putative polyadenylation signals and ATTTA sequences and to include plant preferred codons.") These are just some of the examples that demonstrate that the application contains clear basis for claims directed to "designing a nucleotide sequence." Incidentally, the interference also involved "designing" claims that the withheld review by the Board.

**G. Limitations pertaining to the maximum number of "problem sequences."**

The Patent Office's final basis for rejection stated, "Neither the instant specification nor the originally filed claims appear to provide support for making any Bacillus derived structural genes containing no more than one, seven or two ATTTA and/or Table II polyadenylation sequences or none at all. The specification, and Examples 1 and 4, only describes doing this in specific Bacillus thuringiensis sequences, not in any one." The applicants respectfully traverse.

The Patent Office already recognizes that Examples 1 and 4 provide basis for the claim terms that limit the maximum number of problem sequences in the resulting gene. Other examples also provide support. Example 2 describes an experiment in which a synthetic insecticidal fragment (amino acids 1-615) of Btk HD-1 was made that was devoid of ATTAA sequences and substantially devoid of Table II polyadenylation signal sequences (in this instance, only one). Claims 72 and 76 recite that the claimed structural gene contains no more than one occurrence of the sequence ATTAA or/and no more than one occurrence of the polyadenylation signal sequences listed in Table II. These embodiments finds support, e.g., in Figure 1; at page 23, line 28, to p. 24, line 2; and in Example 2 (p. 50, lines 25-27). The recitations in claims 71 and 74 of no more than seven polyadenylation sequences and no more than seven ATTAA sequences find support, e.g., at p. 39, lines 27-31, and p. 42, lines 8-10. The recitation in claim 75 of no more than two poladenylation sequences finds support, e.g., in Example 3 at p. 53, lines 15-17.

Such examples provide explicit written description support for the claim limitations in the question, and the Patent Office has cited no authority to the contrary. A practitioner in the field of the invention who read the application would understand that these excerpts reflect embodiments of the invention, and provide basis for the claim limitations at issue.

#### **H. Conclusion**

For all of the foregoing reasons, the rejections alleging lack of written description or “new matter” should be withdrawn.

#### **V. THE REJECTION ALLEGING LACK OF ENABLING DISCLOSURE SHOULD BE WITHDRAWN.**

At pages 4-6 of the Office action, the Patent Office rejected claims 47-199 [sic: 119?] under 35 U.S.C. §112, first paragraph, alleging that the disclosure was not enabling for these claims. As its basis for rejection, the Patent Office alleged that checking for P-signals and 30 bp long A+ T-rich regions was “critical or a central” to the practice of the invention, but not included in the claims. The Patent Office cited Figures 1A and 1B, and page 23, line 17, to page 24, line 18, of the application as allegedly supporting this determination. The applicants respectfully traverse.

The application does not describe these approaches as critical, and to the contrary, clearly states that it is merely an *alternative approach*. For example, the paragraph bridging pages 22-23 describes the method of the invention as involving the modification of an existing structural coding sequence which codes for a particular protein by removal of ATTTA sequences and putative polyadenylation signals by site directed mutagenesis. The application does not require that all of the putative problem sequences be removed, but explains that it is most preferred that substantially all of these polyadenylation signals and ATTTA sequences are removed. It also explains that enhanced expression levels are observed with only partial removal of either of the above sequences. Then, at pages 23-24 (the section cited by the Patent Office) the application describes, as "*another embodiment of the present invention*," the flow diagram of Figure 1 and the methodology that it represents. In the various paragraph cited by the Patent Office, the application explains that the Figure 1 method "is somewhat less rigorous than the method first described above." (See lines 20-22.) Thus, the application makes clear that, not only is the paragraph in question not describing a critical embodiment, but it is actually describing a "somewhat less rigorous" embodiment.

Examples 1-4 of the application provided further, direct evidence that the Figure 1 methodology is not critical to practicing the invention. Specifically, Example 4 demonstrates, using an insect challenge assay, the efficacy of methods of the invention based on removal of the polyadenylation signal sequences and the ATTTA sequences, without resort to the Figure 1 alternative embodiments.

Because the application does not describe the Figure 1 methodology as critical, and in fact demonstrates that it is not critical, the rejection for lack of enablement should be withdrawn.

## **VI. THE REJECTION OF CLAIMS 47-119 FOR ALLEGED LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN.**

In paragraph 7 at pages 5-6 of the office action, the Patent Office rejected claims 47-119, alleging lack of written description. The applicants respectfully traverse.

**A. A *Bacillus thuringiensis* Cry endotoxin or other specific nucleic acid is not essential to operation of the claimed invention.**

The Patent Office alleged that *Bacillus thuringiensis* Cry endotoxin sequences are essential to the operation of the claimed invention, and alleged that the claims were overbroad as being directed toward use of a genus for any insecticidal proteins from any *Bacillus* species. In fact, the method described in the application as the invention is described as being much more broadly applicable than the Patent Office acknowledges, or than is presently claimed. As already explained above, the invention is generally applicable for making new structural genes for any protein,<sup>2</sup> and it is especially applicable for making structural genes for proteins derived from *Bacillus*, because bacteria of the genus *Bacillus* have genomes that are unusually rich in adenines and thymidines [(A+T)-rich].

In the approach that is presently claimed, the invention involves removing polyadenylation signal sequences and/or ATTAA sequences (problem sequences). The sequence ATTAA consists entirely of adenines and thymidines. It will be apparent from Table 2 (page 36 of the application) that polyadenylation signal sequences targeted for removal also are predominantly adenines and thymidines. Because the specified problem sequences are themselves (A+T)-rich, they are apt to occur with greater frequency in an (A+T)-rich genome. Page 16, line 15, to page 17, line 9; and at page 21, line 1, to p. 22, line 12, explain that the invention is particularly applicable to genes of *Bacillus*, which have among the most (A+T)-rich genomes and, consequently, a greater propensity for (A+T)-rich problem sequences.

**B. The claims at issue are methods, and the methods are adequately described.**

The Patent Office additionally alleges that the only structures described in the specification are a few *Bacillus thuringiensis* Cry endotoxin coding and amino acid sequences, and alleges that the specification does not describe the structural features of the full scope of insecticidal proteins from any *Bacillus* species. These observations are misguided, and do not support a rejection.

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<sup>2</sup> See, e.g., p. 17, lines 5-10 ("[I]t should be understood that the present method may be used to prepare synthetic plant genes which encode non-plant proteins other than the crystal protein toxin of *B.t.* as well as plant proteins . . .")

**1. The "starting with" step is adequately described under an "essential elements" analysis.**

First, the patent laws do not impose a requirement to describe the structural features of the full scope of any genus for these claims, because a particular nucleic acid is not essential to the claimed invention. With respect to some inventions that are chemical or biological products, it may be important to describe a representative number of species of molecules in order to claim a genus of chemical or biological molecules, because in such circumstances the invention is the molecules. However, it is important to remember that the written description requirement pertains to what is claimed. (Compare *Capon v. Eshhar*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005) and *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006), in which the Federal Circuit clarified that its prior decisions interpreting the written description requirement in the context of genetic inventions do not require applicants to report or describe genes or DNA regions when the claimed inventions are not those DNA regions *per se*, but the novel combinations of elements that include those DNA regions.) The present claims are not directed to a genus *per se*, and are not directed to molecules at all.

Rather, the present claims are directed to a method. In the method, a coding sequence is used as a starting material on which to practice methods steps. For example, claim 47 involves reducing the number of ATTTA sequences or the number of Table II polyadenylation signal sequences that are found in the coding sequence. It is not disputed that the application adequately describes the nature of these problem sequences and multiple approaches for reducing/removing them (for example, claim 47 specifies substituting codons). A step of claim 47 specifies making a structural gene that comprises a coding sequence that includes the substituted codons. It is again undisputed that the application adequately teaches how to make a structural gene sequence, using techniques such as *de novo* synthesis or site-directed mutagenesis of an existing sequence. Thus, the individual method steps, and the claims as a whole, are adequately described.

An analogy can be drawn (for written description purposes) between the current claims and a claim directed to a method of screening that involves starting with essentially any compound and assaying the compound according to particular steps to determine if the compound has a particular biological or chemical property. The Patent Office routinely allows such screening claims, without limitation as to the starting material. The reason, of course, is

that no particular starting material is essential to the screening method; an adequate written description of such a claim depends on whether the steps of the method are adequately described. A particular starting material is not an essential element of a screening claim. That is also the appropriate analysis here.

The Patent Office's own Written Description Training Materials are in complete accord with the foregoing analysis. In particular, Example 18 of the Training Materials is directed to a hypothetical "Process claim where the novelty is in the method steps." The hypothetical presented is that a specification teaches a method for producing proteins using a structural gene for essentially any protein and mitochondria from the fungus *Neurospora crassa*. In the method, mitochondria are isolated from this fungus and transformed with a mitochondrial expression vector which comprises a nucleic acid encoding a protein of interest. The protein is subsequently expressed, the mitochondria is lysed, and the protein is isolated. The specification exemplifies the expression of β-galactosidase using the claimed method using a cytochrome oxidase promoter. In the hypothetical specification, the β-galactosidase is the only exemplified protein produced.

Claim 1 in this hypothetical reads, "A method of producing a **protein of interest** comprising: obtaining *Neurospora crassa* mitochondria, transforming said mitochondria with a expression vector comprising **a nucleic acid that encodes said protein of interest**, expressing said protein in said mitochondria, and recovering said protein of interest." (Emphasis added.)

The Patent Office purposefully made the genus of coding sequences in the method claim of the hypothetical as broad as possible, to make an important point about the application of the written description requirement to the starting materials recited in method claims. The term "nucleic acid that encodes said protein of interest" in the hypothetical claim literally embraces any naturally occurring coding sequence, or for that matter, any artificial coding sequence for any protein. Still, the method claim is adequately described.

The Patent Office's "Analysis" of the written description issue posed by this hypothetical focuses, properly, on the essential elements of the claim, which are the details of the method steps, not the scope of the term "nucleic acid that encodes said protein of interest":

A review of the specification reveals that *Neurospora crassa* mitochondrial gene expression is essential to the

function/operation of the claimed invention. **A particular nucleic acid is not essential to the claimed invention.**

A search of the prior art reveals that the claimed method of expression in *Neurospora crassa* is novel and unobvious.

The claim is drawn to **a genus**, i.e., any of a variety of **methods** that can be used for expressing protein in the mitochondria.

There is actual reduction to practice of a single embodiment, i.e., the expression of β-galactosidase.

The art indicates that there is **no substantial variation within the genus because there are a limited number of ways to practice the process steps** of the claimed invention.

The single embodiment is representative of the genus based on the disclosure of *Neurospora crassa* mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene expression art. One of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

(Emphasis added in bold.)

The Patent Office's "Conclusion" on the question of written description of this claim is unequivocal: "The claimed invention is adequately described."

This hypothetical prepared by the Patent Office makes crystal clear that the description requirement for a starting material in a method claim is minimal where, as here, the starting material is not essential to the claimed invention.

Compared to this hypothetical application and claim, the specification of the current application actually provides a much more compelling case for the conclusion that *the claim is adequately described*. For example, the present specification provides numerous examples, whereas the specification in the hypothetical contained only a single example. Also, the breadth or scope of starting materials recited in the current claim is smaller than the breadth or scope of starting materials in the hypothetical. Importantly, a particular nucleic acid is not

essential to the description of the invention of the present application, much like in the hypothetical in the Patent Office's training materials. The specification robustly describes the important elements of the method steps, such as the description of the problem sequences and the description of how to eliminate them so that their numbers are reduced. Thus, the basis for rejection should be withdrawn.

**2. The claim limitation is adequately described because a person of ordinary skill would be able to start with a sequence derived from *Bacillus***

The office action alleges that the specification does not describe the structural features of the full scope of insecticidal proteins from any *Bacillus* species. The Patent Office's analysis is misdirected, because the invention is not directed to a genus of sequences. Rather, the invention is directed to a method.

In the interview, the examiner expressed the concern of whether a person would be able to determine whether a particular sequence is derived from *Bacillus*. This, too, is not a relevant inquiry because the invention is not directed to a method of differentiating *Bacillus* sequences from non-*Bacillus* ones. Instead, the claims are directed to a method of making a structural gene. Some of the method claims specify *starting with* a sequence derived from *Bacillus*. At the time that the application was filed, a person of ordinary skill in the art could *start with* a sequence derived from *Bacillus*. Exemplary embodiments for the step include getting a sequence from a publication or database that identifies/classifies the sequence as being from *Bacillus* (wild type or modified); and getting a sequence from a bacterial source.<sup>3</sup>

The application exemplifies starting with multiple classes of sequences derived from *Bacillus*, such as wildtype nucleotide sequences, deduced amino acid sequences, and manipulated sequences such as truncation/fragment sequences and hybrids of two or more sequences.

Because the application describes and enables a step of starting with a sequence derived from *Bacillus*, the rejection is improper and should be withdrawn.

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<sup>3</sup> The field of bacteriology was sufficiently mature at the time the invention was filed that the person of ordinary skill could confirm that a source bacteria was a member of the genus *Bacillus*.

**C. Written description of *B.t. Tenebrionus***

Presumably referring to claim 89, the Patent Office rejected claims that specify that the starting sequence be derived from *B.t. tenebrionus*, alleging that the specification does not describe the structural features of any insecticidal protein from such species. This basis for rejection is both factually incorrect, and legally improper.

Example 5 of the application pertains to a *B.t. tenebrionus* sequence on a modification of it according to the invention. Thus, the rejection is factually incorrect. The specification does describe an insecticidal protein from this species.

Also, as explained in the preceding subsection, the present invention is directed to a method, and the adequacy of written description should be evaluated based on the method steps. At the time that the application was filed, a person of ordinary skill in the art was capable of identifying bacteria of the species/strain *B.t. tenebrionus*, and isolating coding sequences from it. No more is required to satisfy the written description requirement of the present method claims. As succinctly stated in a Patent Office's training materials, "A particular nucleic acid is not essential to the claimed invention."

**D. An A+T content of about 62%.**

Presumably referring to claim 79-80, the Patent Office rejected claims on the basis that, "the specification does not describe any starting coding sequences or wild-type *B. thuringiensis* that have an A+T content of about 62%." The specification, at page 21, lines 5-10, explains that *Bacillus thuringiensis* genes are very rich (approximately 62%) in adenine and thymine, especially compared to plant genes and most bacterial genes which have been successfully expressed in plants, which are on the order of 45-55% A+ T. In other words, a person of ordinary skill would expect many starting coding sequences from *Bacillus thuringiensis* to have an A+T content that satisfies the limitation of the claim.

In addition to this explicit discussion of "about 62%" A + T content, the application also describes and supports this claim limitation by way of the native sequences themselves that are exemplified. For example, the Bacillus sequences set forth in SEQ ID NOs: 2, 4, 6, 10, 15, 17, and 19 of the application have A+T contents of 62.5%, 62.7%, 62.4%, 60.9%, 63.9%, 65.2%, and 61.1%, respectively. Thus, the description and the examples support the claim limitation in question. This basis for rejection, too, must be withdrawn.

## VII. THE REJECTIONS THAT ALLEGE INDEFINITENESS SHOULD BE WITHDRAWN.

On page 6 of the Office action, the Patent Office rejected claims 47-58 and 63-111, alleging that these claims were indefinite. The first basis for rejection alleged that claims 47-58 were indefinite because the terms "reduced" and "reducing" are relative terms that render the claim indefinite. The Patent Office asks, "What are they reduced relative to?"

### A. The term "reducing" is not indefinite as used in the claims.

If the claims in question are read as a whole, rather than selecting individual words in isolation, it is impossible to find them indefinite. For example, step (b) of claim 47 recites, "reducing the number of said ATTAA sequences or the number of said polyadenylation signal sequences *in the coding sequence....*" (Emphasis added.) The clear antecedent basis for "in the coding sequence" is the coding sequence with which one starts, introduced in the preceding step (a). Thus, one need not look to the specification to determine what the problem sequences are reduced "relative to"; the claim clearly explains what the problem sequences are reduced relative to. The problem sequences are reduced, relative to the number of problem sequences in the starting sequence. A similar analysis applies to the other rejected claims.

The Patent Office also expresses concern that the specification does not provide a standard for ascertaining the requisite degree of reduction needed to satisfy these terms. It is axiomatic that claim terms should be given their broadest reasonable meaning. In other words, any reduction in the number of the specified problem sequences would be sufficient to meet the "reducing" limitation (assuming that the other limitations of the claim also are satisfied).

### B. The term "substantially devoid" is not indefinite as used in the claims.

The Patent Office rejected claims 63-67, 112, and 1 17-118, alleging that the claim recitation "substantially devoid" is a relative term that renders the claims indefinite. The Patent Office asks, "[W]hat level of reduction is considered 'substantial'?"

At the outset, it should be noted that the claims at issue specify "substantially devoid," not "substantially reduced." Thus, the question of what *level of reduction* is considered substantial is not necessarily relevant to interpretation of any claim.

The plain meaning of the term "devoid" (in the context of the claims) is that something is entirely absent. Thus, a coding sequence is devoid of polyadenylation signal sequences if polyadenylation signal sequences are entirely absent from the coding sequence. Likewise, a coding sequence is devoid of ATTTA sequences when ATTTA is entirely absent from the coding sequence.

The plain meaning of "substantially" is that it modestly broadens the absolute nature of the term "devoid." Thus, a coding sequence is "substantially devoid" of a problem sequence if the coding sequence contains only one or a few of the problem sequences. Stated differently, removal of substantially all occurrences of a problem sequence renders the resulting coding sequence "substantially devoid" of the problem sequence. The term is consistent with teachings throughout the application that the problem sequences are present in the wild type sequences and their numbers should be reduced or substantially eliminated. See, e.g., page 22, line 24, to p. 23, line 13 ("it is most preferred that substantially all of the polyadenylation signals and ATTTA sequences are removed...."). For the avoidance of any doubt, claims that specified "substantially devoid" of a problem sequence have been amended to state "devoid or substantially devoid" of the problem sequence. Thus, it is clear that these claims are intended to cover situations where all, or almost all, of the occurrences of a problem sequence have been removed.

A person of ordinary skill in the art would understand what is meant by substantially devoid, and the application provides guidance. For instance, Example 2 describes an experiment in which a synthetic insecticidal fragment (amino acids 1-615) of Btk HD-1 was made that was devoid of ATTTA sequences and substantially devoid of Table II polyadenylation signal sequences (in this instance, only one). Example 3 describes experiments in which genes encoding chimeric insecticidal proteins were constructed using sequences derived from *Bacillus*. For example, the inventors took the 5' two-thirds of a synthetic HD-1 gene and combined it with the 3' one-third of an HD-73 sequence, modified via site-directed mutagenesis. The resulting construct was devoid of ATTTA, and substantially devoid (reduced in this example from 18 to 2) of Table II polyadenylation signal sequences, and it encoded an *insecticidal hybrid protein* comprised of a fusion of fragments of more than one insecticidal protein derived from *Bacillus*.

The MPEP explicitly acknowledges that relative terminology does not automatically render a claim indefinite. In fact, such terminology has repeatedly been found to

be definite by reviewing courts. In fact, Section 2173.05(b), subpart D, of the MPEP cites cases in which the term "substantially" has been held to be definite within the meaning of §112, second paragraph, of the statute.

### **VIII. THE REJECTION ALLEGING THAT CERTAIN CLAIMS ARE OBVIOUS SHOULD BE WITHDRAWN.**

At pages 7-8 of the Office action, the Patent Office rejected claims 47-70, 81-82, 84-85, 87, 88, 93-100, 102-104, 106-107, 109-119, alleging that the subject matter of these claims was obvious in view of Beremand et al., U.S. Patent Number 4,888,282 (Beremand)<sup>4</sup> in view of Fischhoff et al., 1987, Bio/Technology, 5: 807-813 (the Fischhoff publication). The applicants respectfully traverse for all of the reasons set forth below (any one of which is sufficient to negate the rejection). In subsection A, the Applicants explain why Beremand has been antedated as a reference, necessitating withdrawal of *any* rejection based on that reference, alone or in combination with other references. In the remaining subsections, the Applicants explain that even if Beremand were citable as a reference, the rejection itself lacks merit, and should be withdrawn. Most of the Applicant's remarks in these sections are directed to the deficiencies in the Beremand reference, because the Examiner alleges that Beremand provides the teachings or suggestions for gene synthesis/modification, and relies on the Fischhoff publication only for providing exemplary *Bacillus thuringiensis* endotoxin sequences.

#### **A. Beremand is not effective prior art against the present application.**

The Patent Office's apparent statutory basis for citing the Beremand patent as prior art is 35 USC §102(e). However, the evidence already of record establishes invention by Fischhoff prior to the filing date of Beremand, necessitating withdrawal of any rejection based on Beremand.

With respect to conception, The Board of Patent Appeals and Interferences has already made finding that the evidence "clearly and convincingly" shows that Fischhoff conceived of an invention of amended Count 2 of the interference in which this application was involved no later than December 12, 1986. (See opinion of the US Patent and Trademark Office

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<sup>4</sup> Beremand appears to qualify as a reference only under §102(e), and the applicants reserve the right to attempt to antedate this patent to remove it as a reference.

Board of Patent Appeals and Interferences in *Barton v. Fischhoff v. Adang*, Interference No. 103,781, paper number 255, pages 2, 53 and 64-83.) Similarly, the Board has already found that the evidence of record in the interference clearly and convincingly shows that Fischhoff reduced the invention of Count 2 to practice no later than August 10, 1988. (Id. at pages 2, 53, 54-64.)

Fischhoff's case for priority in the interference proceeding included a brief of 174 pages, thirteen supporting declarations from scientists, 396 exhibits, and a lengthy supporting record of notebooks and other documents totaling more than 1500 pages, which collectively demonstrated that Fischhoff was diligent from Fischhoff's date of conception until Fischhoff's date of reduction to practice. Because of the evidentiary shortcomings of the senior party Adang's/Mycogen's case for priority, the Board awarded priority to Fischhoff without making an official finding that Fischhoff was diligent during a period spanning conception to reduction to practice. However, the Board did note, "Adang does not deny Fischhoff's argument that the evidence of record establishes that Drs. Fischhoff and Perlak worked diligently from October 30, 1986, the alleged date of the written memorandum in which they memorialized their conception of every feature of the invention of Claim 3 of Fischhoff's involved application corresponding to Count 2, until they actually reduced an embodiment thereof to practice no later than September 9, 1988, allegedly no later than August 10, 1988...."

Based on Fischhoff's 1986 conception and diligence reducing the invention to practice, Fischhoff was a prior inventor who has antedated the Beremand reference (filing date June 4, 1987). Because Beremand is unavailable as a reference, the Patent Office should withdraw any rejection based in whole or in part of Beremand.

**B. Beremand has nothing to do with creating or modifying a coding sequence to increase gene expression.**

The Supreme Court has instructed that the "objective" test for unobviousness requires a determination of the scope and content of the prior art, and ascertainment of the differences between the prior art and the claims. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. \_\_, 82 USPQ2d 1385 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1996)). In an obviousness inquiry, references must be analyzed in their entirety for what they would have taught to one of ordinary skill, without the benefit of hindsight. The references must be read for what they would have taught a person of ordinary skill in the art who is unfamiliar with the invention that is currently being claimed and analyzed for obviousness. Without the benefit of

hindsight, it is clear that the Beremand reference was directed to solving completely different problems from the invention that is presently claimed, and the profound differences between the cited art and the claims render the claims unobvious.

The “background” section of Beremand provides guidance as to the purpose behind Beremand, and that purpose has nothing to do with the present invention. Beremand explains that the acyl-carrier protein (ACP) has been the focus of intensified research because it may serve as a marker for studies of the regulation of plant fatty acid synthetase gene expression, which studies may eventually have an important practical impact on the selection of genetic engineering strategies for modification of the amount and type of fatty acids produced by oilseed crops. (See column 1, lines 7-31.) Beremand explains that, as far as its inventors understood, acyl carrier proteins were the first proteins in plant fatty acid biosynthesis to have been purified to homogeneity, and to date, were the only such proteins for which amino acid sequence data was available. (See column 1, lines 33-37.) Beremand also explained that plants were known to contain multiple isoforms of this enzyme, and predicted that the isoforms may be coded by multi-gene families. (See column 1, lines 53-61.)

The purpose of Beremand is clear from the end of the “background” section. There, Beremand explains that acyl carrier proteins constitute less than 0.1% of the total cell protein in most species, making purification difficult, and hampering studies of this important enzyme. "Expression of a plant ACP in a suitable vector such as *E. coli* might provide a means of providing sufficient ACP for enzymological and other studies. A synthetic gene encoding only a structural protein is more likely to produce an active ACP when introduced into *E. coli* than either a genomic clone (with expected intervening sequences, i.e., introns) or a full-length cDNA clone (with an expected transit peptide encoding sequence)." (See column 2, lines 10-26.) Thus, the purpose of the Beremand invention was to provide a synthetic structural gene encoding a *plant protein* (spinach leaf ACP-I, the only such enzyme for which a plant amino acid sequence was known) that would be free of introns and free of transit peptide sequences, to permit robust recombinant production of the protein in *E. coli*, a *non-plant host cell*.

Beremand's description of the invention is entirely consistent with the purpose set forth at the end of the background section. For example, Beremand explained that their codon selection was made "in order to optimize the synthetic gene as a probe for the naturally occurring homologous gene and mRNA." (See column 4, lines 57-61. See also column 5, lines 38-40:

"the full-length synthetic ACP genes contemplated by this invention have utility as sensitive DNA and RNA probes to the ACP gene.") Beremand also describes using the synthetic gene to express the encoded protein in *E. coli*. (See column 10, lines 1-19.)

Notably absent from Beremand is any discussion of the problem of expressing non-plant genes in plant expression systems. Notably absent from Beremand is any discussion of the problem of ATTTA sequences when trying to express non-plant genes in plant expression systems. Notably absent from Beremand is any discussion of the problem of polyadenylation signal sequences when trying to express non-plant genes in plant expression systems. Notably absent from Beremand is any direction that the expression of a non-plant gene in a plant might be enhanced by synthesizing or modifying the gene so as to avoid these problems sequences. All of the pending claims recite one or more elements or steps based on these unobvious features that are absent from Beremand (and not supplied by the secondary reference).

**C. A person of ordinary skill in the art, at the time of the present invention, would have had no motivation to combine Beremand with the Fischhoff publication.**

The Patent Office characterized Beremand as a document that taught codon optimization, and alleged that it would have been obvious at the time the invention "to modify the method of codon optimization as taught by Beremand et al, to codin-optimizes [sic] the truncated or full-length HD-1 sequence described in Fischhoff et al." The Patent Office characterized the Fischhoff publication as concerned with the problem of expressing a *Bacillus thuringiensis* endotoxin HD-1 in plants using a chimeric gene that comprises a plant promoter, a *Bacillus thuringiensis* endotoxin HD-1 and polyadenylation sequence. To explain why a person of ordinary skill would have been motivated to combine these references, the Patent Office asserted that Fischhoff teaches the level of expression of the HD-1 mRNA was very low, and that the unmodified form may be unstable. Thus, the Patent Office's alleged motivation to combine the references contains an *unstated assumption* that a person of ordinary skill in the art would have seen some connection between Beremand's reasons for codon selection and Fischhoff's problem of expressing a bacterial gene in a plant cell. That assumption is incorrect, based wholly on hindsight knowledge of the current application.

The Fischhoff publication, cited as the secondary reference, did not teach or suggest codon substitutions as the solution for the problem of low expression, or for any other purpose.

Beremand chose *plant codons* for the purpose of making a gene probe in hopes of *locating ACP genes in plant genetic material*. (See discussion above and at Column 5, lines 38-40 of Beremand.) Beremand chose codons *from a codon table from the same kingdom of organism (plants) as the amino acid sequence* with which Beremand was working because Beremand was presented with a somewhat uncommon fact situation in which Beremand was in possession of an amino acid sequence of a plant ACP protein, but was not in possession of a plant cDNA or genomic sequence encoding the protein. The Fischhoff publication, in contrast, presented the more common scenario where the authors were already in possession of both a wild type coding sequence and a deduced amino acid sequence. Thus, a fair characterization of Beremand (absent hindsight) is that Beremand provided a suggestion for using codon biases to locate a cDNA (or genomic DNA) when one is in possession of an amino acid sequence for the protein whose gene is being sought. The Fischhoff publication did not present this problem, and there would have been no motivation to combine the two documents to look for a solution to any problem.<sup>5</sup>

Even if, for the sake of argument, one were to try to find a solution to the problem of poor gene expression that faced the authors of the Fischhoff publication, one would not combine the Fischhoff publication with the Beremand patent. There is nothing in Beremand to suggest that plant codon optimization would be beneficial for expression of a bacterial gene in a plant, the subject of the Fischhoff publication. Again, Beremand involved the use of plant codons for a synthetic gene for a plant protein. Thus, the Patent Office's alleged motivation for combining these two documents does not withstand scrutiny, and is clearly based on a hindsight reconstruction of the present invention.

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<sup>5</sup> There is also no prior art of record that suggested the existence of plant homologs of the *Bacillus thuringiensis* endotoxin HD-1, such as would have motivated a person to combine Beremand with the Fischhoff publication to make a plant-codon optimized probe for screening plant genetic material for a plant homologue of a *Bacillus thuringiensis* endotoxin HD-1 gene sequence.

**D. There would have been especially no motivation to combine Beremand and Fischhoff in relation to methods that start with a coding sequence.**

As explained in the two preceding subsections, Beremand involved an uncommon situation in which a plant protein's complete amino acid sequence was available, but no cDNA or genomic sequence was available. Beremand presented an approach for making a synthetic coding sequence based on the amino acid sequence.

The Fischhoff publication presented a situation where a coding sequence already existed. There would have been no motivation, when starting with a coding sequence, to look to the Beremand document.

A number of the current claims are directed to methods that involve starting with a coding sequence. See, e.g., claims 47-58, 67-68, 69, 112, and claims dependent thereon. Again, there would have been no motivation to look to the Beremand publication for guidance when starting with the coding sequence because the Beremand publication provided no guidance for making modifications once in possession of a coding sequence.<sup>6</sup> Similarly, rejected claim 110 specifies that the making step comprises performing site-directed mutagenesis on a coding sequence. The Beremand publication related to a situation where no starting coding sequence existed at all, so it would not have been consulted or combined with a reference in the context of having a starting sequence and performing site-directed mutagenesis.

**E. Even if the teachings of Beremand and the Fischhoff publication or combined, the present invention would not have been obvious.**

Even if, for the sake of argument, one were to combine the teachings of Beremand and the Fischhoff publication, one would not have arrived at the claimed invention. The combination simply fails to disclose or suggest numerous limitations of the claims. Notably absent from Beremand is any discussion of the problem of expressing non-plant genes in plant expression systems. Notably absent from Beremand is any discussion of the problem of ATTAA sequences when trying to express non-plant genes in plant expression systems. Notably absent from Beremand is any discussion of the problem of polyadenylation signal sequences when trying to express non-plant genes in plant expression systems. Notably absent from Beremand is

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<sup>6</sup> The Patent Office has not alleged that Beremand's teachings to remove intron or transit peptide sequences to improve expression in *E. coli* are relevant to the rejection, and they certainly do not disclose or suggest any aspect of the claimed invention.

any direction that the expression of a non-plant gene in plants might be enhanced by synthesizing or modifying the gene so as to avoid these problem sequences. The teachings of the Fischhoff publication, when combined with Beremand, do not remedy these shortcomings.

The Patent Office tries to address this clear shortcoming by identifying two codons in the gene sequence of the Fischhoff publication which, if modified using preferred codons in Beremand, would result in the elimination of one ATTTA and one polyadenylation signal sequence. Unfortunately, the only basis for selecting the two specific codons was improper hindsight, based on the knowledge of the present application that these two types of sequences are problem sequences in the *Bt* gene. The references relied upon for the current rejection do not point a person of ordinary skill to these particular codons.

Moreover, the Patent Office's statement of the rejection failed to consider whether every limitation of every rejected claim was satisfied. For example, claim 47 and many other rejected claims specify reducing the number of a problem sequence. The Patent Office identified one problem sequence in a large coding sequence and alleged that the one sequence would be eliminated, but did not establish that the total number of the problem sequences would be reduced. In other words, the Patent Office has not established that the combination of references would result in a net reduction of either of the types of problem sequences in the gene as a whole.

Similarly, claims 63, 112, and other rejected claims specify making a structural gene that is substantially devoid of ATTTA sequences or polyadenylation signal sequences. The Patent Office has not established, by pointing to an alleged elimination of one ATTTA or polyadenylation signal sequence, that the combined teachings of the two documents would result in a coding sequence that is substantially devoid of either type of problem sequence.

Similarly, claims 67 and other rejected claims include a step that requires combining coding sequences that encode portions of one or more insecticidal polypeptides. The Patent Office did not establish (or even allege) in its rejection that the cited references (alone or in combination) disclose or suggest this method step.

Dependent claims 103-104 further specifies reducing the number of regions in a coding sequence with greater than five consecutive adenine & thymine (A+T) nucleotides. The Patent Office has not established, or even alleged, that the cited references (alone or in combination) disclose or suggest this step.

**F. A combination of Beremand with the Fischhoff publication would have led the person of ordinary skill in the art away from the claimed invention.**

Even if there were a motivation to combine Beremand's codon selection with Fischhoff's goal of improved gene expression, the prior art did not create any reasonable expectation of success. The only "expectation" suggested by Beremand for a synthetic gene constructed with preferred codons from a plant codon table was an expectation of obtaining a better hybridization probe for screening for a wild type gene within the plant genetic material. Beremand teaches nothing about the effect of preferred codons on gene expression and creates no expectation that codon selection would be result-effective for improving expression of genes that do not express well in plants.

In fact, if a person of ordinary skill were to read Beremand as teaching codon optimization to benefit gene expression, the person would have been *led away* from the current invention. This is because Beremand was choosing plants codons to make a synthetic gene encoding a plant amino acid sequence for eventual expression in *E. coli*. In other words, *Beremand used a codon table from the source organism*, not a codon table from the transgenic host organism in which the gene was going to be expressed. Because Fischhoff's source organism was *Bacillus thuringiensis*, a person following the teachings of Beremand would have been motivated to use *Bacillus thuringiensis* codons to express Fischhoff's *B.t.* amino acid sequence. Likewise, if the person of ordinary skill were "optimizing codons" for Beremand's true purpose -- for use as a probe to identify genes in a host organism in which the genes were expected to be found -- the person again would have used *Bacillus* codon tables and would have been directed away from the present invention. A person who combined the teachings of Fischhoff and Beremand in hopes of identifying additional HD-1 crystal protein genes would have been motivated to look in other *Bacillus* bacteria, and consequently would have been motivated to optimize using *Bacillus* codons. The epitome of nonobviousness, of course, is when a combination of the prior art teaches away from the claimed invention. In its recent *KSR* opinion, the Supreme Court reaffirmed the validity of the principle, dispositive in *United States v. Adams*, 383 U.S. 39, 51-52 (1966), that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. See *KSR*, 82 USPQ 2d at 1395, 127 S.Ct. at 1739-40.

**G. Methods that do not require resort to a preferred codon table are unobvious**

All of the pending claims recite a method of making a structural gene that *do not require* the use of a codon table that contains “preferred codons” assembled from a collection of known plant genes.<sup>7</sup> The Patent Office’s rejection alleges that a “method of codon optimization as taught by Beremand” would be obvious. According to the Patent Office, “Beremand et al. disclose that codons of a gene must be matched to that of plants....” Clearly, if Beremand teaches that one “must” resort to plant preferred codons, a method that *does not require* resort to a plant preferred codon table would have been unobvious in view of Beremand. Thus, the present claims, which produce an improved structural gene without a step that requires resort to plant preferred codons, would have been unobvious. *Cf. In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966) (Removal of an element while retaining its function deemed unobvious).

**H. Summary.**

There would have been no motivation to combine the references cited by the examiner. Even if the references were combined, one would not arrive at the method as recited in the claimed invention. In fact, a combination of the references would have had no reasonable expectation or success, and would have let away from the claimed invention. For all of these reasons, the rejection for alleged obviousness should be withdrawn.

**IX. THE REJECTION ALLEGING DOUBLE PATENTING SHOULD BE WITHDRAWN.**

In paragraph 13 of the office action, the Patent Office provisionally rejected claims 47-58 and 67-68 on the ground of nonstatutory, obviousness-type double patenting in view of claims 71-72 of co-pending patent application number 10/102,469.

The claims of the current application are directed to methods. All of the independent claims of the co-pending application are directed to products (e.g., a structural gene). Inadvertently, dependent claims 71-72 of the co-pending application were filed with a

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<sup>7</sup> The present application provides a plant codon table and indicates a preference for avoiding codons rarely found in plants, but neither the application nor the current claims requires resort to a plant codon table to practice the method successfully.

preamble that recites, "The method according to...." This error has been corrected in the co-pending application, which should render moot the double patenting rejection.

In the event that the foregoing amendment does not render moot the rejection, the applicants respectfully request that the double patenting rejection be held in abeyance, at least until such time that it is more than a provisional rejection, e.g., at such time as the claims in both applications are deemed to be allowable.

## X. CONCLUSION

Prompt, favorable consideration of the application is respectfully requested. The applicants request the opportunity to resolve any minor issues by telephone to expedite allowance. The Patent Office is authorized to charge any fee deficiencies necessary for entry of this submission, and other fees that may arise in this case (other than the issue fee) to deposit account no. 13-2855, under order number 28079/41785.

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Respectfully submitted,

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